

established that the use of S-nitrosothiol compounds to treat female sexual dysfunctions is patentable over the prior art.

Independent claims 61 and 62, respectively, of the present application read:

61. **A method for treating female impotence** in a female individual in need thereof comprising administering to the female individual a therapeutically effective amount of a composition comprising an **S-nitrosothiol** compound and a pharmaceutically acceptable carrier. (Emphasis added)

62. **A method for treating female impotence** in a female individual in need thereof comprising **topically** administering to the female individual a therapeutically effective amount of a composition comprising an **S-nitrosothiol** compound and a pharmaceutically acceptable carrier. (Emphasis added)

The claims of the present application (priority date September 18, 1996) were pending at the time of issuance of U.S. Patent No. 6,308,841, (priority date October 28, 1997) and are **substantially the same** as the claims in issued U.S. Patent 6,306,841.

As stated in MPEP 2307.02:

When claims corresponding to claims of a patent are presented, the application is taken up at once and the examiner must determine whether the presented claims are patentable to the applicant. If they are not, they should be rejected on the appropriate ground(s). However as long as one of the presented claims is patentable to the applicant and is **claiming the same invention** as at least one claim of the patent, an interference should be declared.

The ground of rejection of the presented claims may or may not also be applicable to the claims in the patent; if it is, **any letter including the rejection must have the approval of the group director**. See MPEP 1003, item 10. (Emphasis added)

As stated above, the claims in Applicant's pending application and the claims in U.S. Patent No. 6,306,841 are **substantially the same**. Thus Applicant's pending application must contain allowable subject matter as the PTO has already issued substantially the same claims in U.S. Patent No. 6,306,841.

Applicants respectfully submit that the Examiner must either allow the present claims and declare an interference or get the approval of the Group Director before issuing another rejection.

II. Rejection under 35 U.S.C. §103

A. Related U. S. Patents

Applicants respectfully disagree with the Examiners assertion on pages 4 and 5 of the Office Action that states:

Applicant argues that the “PTO has already established that the use of compounds to treat male sexual dysfunctions does not render *prima facie* obvious the use of the same compounds to treat female sexual dysfunctions” citing patents (e.g. Patents 5,708,031; 5,718,917; 5,877,216; 5,945,117; 5,770,606; and 5,656,464) and purported prosecution histories involving such patents.

Applicant’s argument is irrelevant to the case at hand since every application stands or falls on its own merit. In any event, it is also noted that applicant’s argument can easily be interpreted as **supporting the above obviousness rejection, since compounds useful in males have been found similarly useful in females (and visa versa) in the treatment of sexual dysfunction.**

(Emphasis added)

Applicants respectfully submit that these issued patents directed to methods for treating female sexual dysfunctions (e.g. female impotence) using compounds that were previously known to be effective for treating male sexual dysfunctions supports Applicant’s position that the use of compounds to treat male sexual dysfunctions **does not render *prima facie* obvious** the use of the same compounds to treat female sexual dysfunctions. These issued patents (U.S. Patent Nos. 5,877,216 and 5,945,117) directed to methods for treating female sexual dysfunctions (e.g. female impotence) using compounds that were previously known to be effective for treating male sexual dysfunctions **were all filed after the priority date of Applicant’s application.** Table 1 that summarizes the priority date of these applications.

Table 1

Female Sexual Dysfunction	
U.S. Patent No.	Priority Date
Present Application	September 18, 1996
5,877,216	October 28, 1997
5,945,117	January 30, 1998

As previously discussed in the Response and Amendment filed September 26, 2001, the discussion of which is incorporated herein in its entirety, the PTO in issuing U.S. Patent Nos. 5,877,216 and 5,945,117, with claims directed to female sexual dysfunction, when it had previously issued U.S. Patent Nos. 5,770,606, 5,718,917 and 5,708,031, with claims directed to the treatment of male sexual dysfunction **with the same compounds**, has clearly established a precedent that claims directed to methods for treating female sexual dysfunctions are **patentably distinct** from methods for treating male sexual dysfunctions with the same compounds.

In further support thereof, as discussed above, U.S. Patent No. 6,306,841, has claims directed to methods for treating sexual dysfunction in females with compounds including S-nitrosothiols. Again this issued U.S. Patent has a priority date of October 27, 1998, i.e. **after** the priority date of the Applicant's application.

In view of the above, Applicants respectfully request reconsideration and allowance of pending claims 61-65 and 70-72.

B. Rejection under 35 U.S.C. §103

Claims 61-65 are rejected under 35 U.S.C. § 103 as obvious over Stamler et al (U. S. Patent No. 5,380,758) in view of Gioco et al (U. S. Patent No. 5,565,466).

As pointed out by the Examiner, Stamler does not disclose or suggest the use of S-nitrosothiols for the treatment of female sexual dysfunctions, and does not provide motivation for one to use S-nitrosothiols for the treatment of female sexual dysfunctions. Additionally, Applicant's respectfully submit that at the time of Applicant's invention, the gender differences in response to nitric oxide was known. Hence to one skilled in the art it would not be obvious

that a nitric oxide donating compound that has been shown to have an effect in males would also have an effect in females.

For example, Jeremy et al., *Circulation*, 94(3): 498-506 (August, 1996), a copy of which is attached hereto as Appendix 4, at page 504, column 1, in the Section entitled “Sex and L-Arginine Response” states:

The degree of impairment of endothelium-dependent vasodilatation was similar in male and female rabbits after 14 weeks, and no preservation of vascular reactivity was seen in the arginine treated females. The extent of atherosclerosis in the ascending aorta was similar in the two sexes, but atherosclerosis in the descending aorta was much less; in females. **Unlike males, there was no evidence of a treatment benefit of L-arginine in females.** This may simply reflect a smaller expected treatment effect in animals with less extensive disease, but **there is also evidence for sex differences in NO metabolism in the aorta**” (Emphasis added)

Nitric oxide is synthesized by the oxidative deamination of a guanidino nitrogen of L-arginine by the enzyme nitric oxide synthase. (Fukuto et al, in *Methods in Nitric Oxide Research*, Feelisch et al., Eds., John Wiley & Sons, Ltd., pages 147-160 (1996)). As shown by Jeremy et al, L-arginine, a compound that generates nitric oxide *in situ*, had a beneficial effect in males but had no effect on females. Hence, one skilled in the art would not conclude that S-nitroso-glutathione, a compound that donate, transfer or release nitric oxide, and can be used to treat male impotence could also be used to treat female impotence or female sexual dysfunction. Thus based on the teachings in Stamler and the level of knowledge in the art of nitric oxide, one skilled in the art would not be motivated to use S-nitrosothiols for the treatment of female sexual dysfunctions.

The Office Action on page 4, states:

The Gioco patent reference provides one of ordinary skill in the art with motivation to utilize S-nitrosothiols to treat female impotency in the same manner as in the treatment of males as disclosed in Stamler, since Gioco teaches that the erectile response in males and females is similar and amenable to similar treatments including the utilization of vasodilation agents which encompass S-nitrosothiols.

Applicants respectfully disagree with the Examiner and respectfully submit that at the time of Applicant's invention the many differences between male and female sexual responses was well recognized by one skilled in the art. Hence one skilled in the art would not have concluded that the treatment for male impotence or male sexual dysfunction would be the same treatment for female impotence or female sexual dysfunction. Additionally, one skilled in the art would not have concluded that a compound that resulted in vasodilation, increased blood flow and engorgement to the gentiles would also have resulted in vaginal length change, vaginal luminal pressure, vaginal lubrication, vaginal pH, hormonal shifts, etc. and effect other factors that are responsible for female sexual dysfunctions or females impotence.

For example, Halvorsen et al., *J. Am. Board Fam Pract.*, 5:51-61 (1992), copy of which was submitted in the Information Disclosure Statement filed on September 26, 2001, at page 52, column 1, line 43 to column 2, line 2, states:

Sexual arousal disorders include (1) female sexual arousal disorder, characterized by failure to attain or maintain the lubrication-swelling response of sexual excitement until completion of the sexual activity or by lack of a subjective sense of sexual excitement and pleasure during sexual activity; and (2) male erectile disorder, marked by failure to attain or maintain erection until completion of sexual activity or by lack of a subjective sense of sexual excitement and pleasure during sexual activity.

At the time of Applicant's invention it was also recognized dyspareunia or painful intercourse is a highly prevalent disorder in females. Rosen et al., *J. Consult Clin. Psychol.*, 63: 877-890 (1995), copy of which is attached hereto as Appendix 5, at page 884, column 1, line 54 to column 2, line 3, states:

Dyspareunia or painful intercourse, is a highly prevalent disorder in women, but it is relatively rare in men. Bancroft (1989) noted that only 1% of men attending a sexual dysfunction clinic in Scotland complained of painful during intercourse, whereas other authors have reported a prevalence rate or 1% to 1.5% of men over the age of 60 (Diokno et al. 1990). In contrast, dyspareunia has been identified as the most common sexual complaint spontaneously reported to gynecologists (sp) (Steege, 1994) and is reported by

10% to 15% of women in community-based surveys (Laumann et al., 1994; Rosen, Taylor, Leiblum and Bachmann, 1993).

Rosen et al at page 885, column 2, begins by stating that:

Less attention has been directed to the treatment of female sexual disorders.

They conclude:

In the clinical area, diagnostic and etiological issues need to be addressed and the value of multidimensional assessment models awaits further evaluation.

At the time of Applicant's invention it was also recognized that an increase in vaginal blood flow and increased vaginal lubrication did not result in an increase in sexual response. *See* for example, Levin, *Exp. Clin. Endocrinol.*, 98(2): 61-69 (1991), copy of which was submitted in the Information Disclosure Statement filed on September 26, 2001. Levin at page 63, lines 35-37, states:

It is interesting to note that infusion of VIP apparently did not cause any of the subjects to report that they felt any sexual arousal despite the fact that the vagina had an increased blood flow and increased lubrication.”

Applicants respectfully submit that at the time of Applicant's invention one skilled in the art did recognize the differences between male and female sexual responses but did not have sufficient models or methods available to assess these differences. Hence one skilled in the art would not have concluded that the treatment for male impotence or male sexual dysfunction would be the same treatment for female impotence or female sexual dysfunction.

Applicants respectfully submit that even today one skilled in the art cannot and would not conclude that the treatment for male impotence or male sexual dysfunction would be the same treatment for female impotence or female sexual dysfunction based on the disappointing results obtained for sildenafil (Viagra®) in women relative to men. As reported by the Doctor's Guide, March 5, 1999, copy of which is attached hereto as Appendix 6, on page 1, lines 1-3:

In the first evaluation of the effects of Pfizer Inc.'s Vaigra (sildenafil) on women, investigators at Columbia Presbyterian Center of New York Presbyterian Hospital found that, unlike men, the drug offers little relief of sexual dysfunctions.

The same conclusion was reached by Meston et al, *Curr Opin. Urol.*, 11:603-609 (2001), copy of which is attached hereto as Appendix 7. They state that sildenafil citrate increases genital blood flow but may not impact on subjective reports on arousal.

Applicants respectfully submit that as acknowledged by Gioco, and supported by the cited art of record, there are many differences between male and female sexual responses. Hence one skilled in the art would not conclude that the treatment for male impotence or male sexual dysfunction would be the same treatment for female impotence or female sexual dysfunction, as discussed above, the discussion of which is incorporated herein in its entirety. Hence one skilled in the art would not be motivated to use S-nitrosothiols for the treatment of female sexual dysfunctions based on the teachings in Gioco.

Additionally nothing in Gioco or the prior art, would lead one to conclude or reasonably expect, that based on the teachings of Stamler that since S-nitrosothiols are useful for the treatment of male impotence, they should also be useful for the treatment of female impotence.

Thus, Stamler in combination with Gioco does not provide any motivation for one to arrive at the presently claimed methods of treating female impotence by administering S-nitrosothiol compounds.

In view of the above, Applicants respectfully submit that the presently claimed invention is unobvious over the cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

III. Obviousness-Type Double Patenting Rejection

Claims 61-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 20-66 of co-pending Application No. 09/280,540, in view of Stamler et al (U.S. Patent No. 5,380,758) and Gioco et al (U.S. Patent No. 5,565,466).

Claims 61-65 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 35-56 of co-pending Application No. 09/306,809, in view of Stamler et al (U.S. Patent No. 5,380,758) and Gioco et al (U.S. Patent No. 5,565,466).

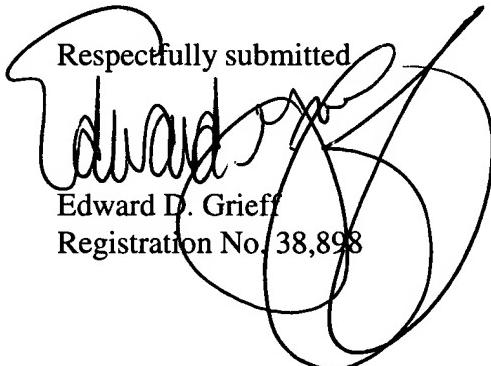
Applicants respectfully request that the Examiner hold these provisional obviousness-type double patenting rejections in abeyance pending a finding of allowable subject matter.

IV. Terminal Disclaimer

In response to the obviousness-type double patenting rejection for claims 61-65 over claims 8-11 of co-pending Application No. 09/354,424 in view of Stamler et al (U. S. Patent No. 5,380,758) and Gioco et al (U. S. Patent No. 5,565,466), Applicants filed a Petition to Withdraw Terminal Disclaimer on April 16, 2002, as claims 8-11 of co-pending Application No. 09/354,424 were cancelled from that application. The Petition was granted on June 17, 2002, and hence the Terminal Disclaimer has been withdrawn.

V. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 61-65 and 70-72. Examiner Celsa is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application.

Respectfully submitted

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Appendix 1- Pending Claims

61. A method for treating female impotence in a female individual in need thereof comprising administering to the female individual a therapeutically effective amount of a composition comprising an S-nitrosothiol compound and a pharmaceutically acceptable carrier.

C1 | 62. (Amended) A method for treating female impotence in a female individual in need thereof comprising topically administering to the female individual a therapeutically effective amount of a composition comprising an S-nitrosothiol compound and a pharmaceutically acceptable carrier.

63. The method of claim 61, wherein the S-nitrosothiol compound is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

64. The method of claim 63, wherein the S-nitrosothiol compound is S-nitroso-glutathione.

65. (Amended) The method of claim 61, wherein the S-nitrosothiol compound is

(i) $\text{CH}_3(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;

(ii) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;

(iii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{B}$; or

(iv) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_x-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

C2 | wherein x is 2 to 20; R_e and R_f are each independently hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, amino, alkylamino, amido, alkylamido, dialkylamino, or carboxy; or R_e and R_f taken together with the carbon atom to which they are attached are carbonyl, cycloalkyl or bridged cycloalkyl; and B is fluoro, $\text{C}_1\text{-}\text{C}_6$ alkoxy, cyano, carboxamido, cycloalkyl, arylalkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro or aryl.

70. (New) The method of claim 62, wherein the S-nitrosothiol compound is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

71. (New) The method of claim 62, wherein the S-nitrosothiol compound is S-nitroso-glutathione.

72. (New) The method of claim 62, wherein the S-nitrosothiol compound is

- (i) $\text{CH}_3(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;
(ii) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;
(iii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{B}$; or
(iv) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_x-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein x is 2 to 20; R_e and R_f are each independently hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, amino, alkylamino, amido, alkylamido, dialkylamino, or carboxy; or R_e and R_f taken together with the carbon atom to which they are attached are carbonyl, cycloalkyl or bridged cycloalkyl; and B is fluoro, $\text{C}_1\text{-}\text{C}_6$ alkoxy, cyano, carboxamido, cycloalkyl, arylalkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro or aryl.

(13)

Appendix 2- Amendments to Claims

Cancel claims 35-60, without prejudice.

62. (Amended) A [The] method [of claim 61,] for treating female impotence in a female individual in need thereof comprising topically administering to the female individual a therapeutically effective amount of a composition comprising an S-nitrosothiol compound and a pharmaceutically acceptable carrier. [wherein the composition is administered topically.]

65. (Amended) The method of claim 61, wherein the S-nitrosothiol compound is

- (i) $\text{CH}_3(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;
- (ii) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;
- (iii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_x\text{B}$; or
- (iv) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_x-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein x is 2 to 20; R_e and R_f are each independently hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, amino, alkylamino, amido, alkylamido, dialkylamino, or carboxy; or R_e and R_f taken together with the carbon atom to which they are attached are carbonyl, cycloalkyl or bridged cycloalkyl; and B is fluoro, $\text{C}_1\text{-}\text{C}_6$ alkoxy, cyano, carboxamido, cycloalkyl, arylalkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro or aryl.

Cancel claims 66-69, without prejudice.

70. (New) The method of claim 62, wherein the S-nitrosothiol compound is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione,

71. (New) The method of claim 62, wherein the S-nitrosothiol compound is S-nitroso-glutathione.

72. (New) The method of claim 62, wherein the S-nitrosothiol compound is

- (i) $\text{CH}_3(\text{C}(\text{R}_e)(\text{R}_f))_x\text{SNO}$;

(ii) HS(C(R_e)(R_f))_xSNO;

(iii) ONS(C(R_e)(R_f))_xB; or

(iv) H₂N-CH(CO₂H)-(CH₂)_x-C(O)NH-CH(CH₂SNO)-C(O)NH-CH₂-CO₂H;

wherein x is 2 to 20; R_e and R_f are each independently hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, amino, alkylamino, amido, alkylamido, dialkylamino, or carboxy; or R_e and R_f taken together with the carbon atom to which they are attached are carbonyl, cycloalkyl or bridged cycloalkyl; and B is fluoro, C₁-C₆ alkoxy, cyano, carboxamido, cycloalkyl, arylalkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro or aryl.